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Status of Marine Biomedical Research*

by Otto Bessey†

A meeting on Marine Biomedical Research, sponsored by the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health and the Smithsonian Institution Museum of Natural History, was attended by approximately 125 scientists, directors and representatives from many of the country's marine biological laboratories, and government agencies whose interests and responsibilities are in the marine biology and health areas. The purpose of the meeting was to explore the undeveloped research opportunities in the area of marine biology for the advancement of our understanding of human health problems and to provide information on the current status of marine biology laboratories. The meeting was devoted to presentations and discussions in four general areas: (1) Marine Species as Models for Human Disease; (2) Environmental Carcinogenesis and Mutagenesis; (3) Human Health and the Marine Environment—infectious agents and naturally occurring and foreign toxins; and (4) Drugs from the Seas. Representatives from twelve of the country's approximately 40 marine laboratories discussed their organization, developmental history, scientific programs, facilities, and present status of their support. The presentations served as a background and stimulated very lively analytical and constructive discussions of the undeveloped research and education potential residing in the marine environment and biological laboratories for a better understanding of many human health problems; some scientific areas that should be developed to realize this potential; and the needs and problems of marine laboratories that require attention and support if they are to survive and realize their possibilities.

Introduction

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The first day of the meeting was devoted to presentations and discussions in four general areas: (1) marine species as models for human disesase; (2) environmental carcinogenesis and mutagenesis; (3) human health and the marine environment—infectious agents and naturally occurring and

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foreign toxins; and (4) drugs from the seas. On the second day representatives from twelve of the country's approximately 40 marine laboratories discussed their organization, developmental history, scientific programs, facilities, and present status of their support.

The presentation served as a background and stimulated a very lively, analytical and constructive discussion of the undeveloped research and education potential residing in the marine environment and biological laboratories for a better understanding of many human health problems; some scientific areas that should be developed to realize this potential; and the needs and problems of marine laboratories that require attention and support if they are to survive and realize their possibilities.

At the end of the conference a small committee was formed to plan and prepare a paper setting forth the scope, goals, problems and needs of marine biological laboratories for the further development of an area which has been referred to as Marine Biomedicine, and to continue the exchange of information among marine biomedical researchers.

Opening Remarks

David P. Rall (National Institute of Environmental Health Sciences): Although many program directors and scientists at NIH have been interested for sometime in the very valuable biomedical research presently ongoing in the Nation's marine laboratories and its potential for development, this interest has been scattered. In addition to NIH's continuing broad interests, NIEHS now hopes to provide a central focus at NIH and to take the initiative in fostering research development in the biomedical aspects of marine biology. This seems a logical step since, as noted from the subject areas in this conference, marine biology has an important and increasing part to play in the solving of problems arising from the adverse effects of environmental factors on the health of man—the area of responsibility for research with which the National Institute of Environmental Health Sciences is charged. NIEHS carries out their research in laboratories located in Research Triangle Park, North Carolina, which is supplemented by contract supported research. In addition, the Institute, through the grant mechanism, supports research throughout the country. Although NIEHS is one of the smallest Institutes at NIH, it is the major source of support for research in the field of environmental health sciences.

Concern with human health is as important, or more so, as the preservation of our ecology as part of the nation's environmental protection effort, and should receive reasonable support. It is clear, however, that within the limits of available resources, it will be impossible to develop programs in all the areas important for a better understanding of those environmental factors which adversely affect man's health. Therefore, it will be necessary to choose among the ongoing programs which ones should be expanded and what new programs should be developed. It is essential that we develop the necessary information so that the wisest and best choice of plans can be made, not only relative to marine biology and the part it might play in environmental problems, but also its relationship in the more general biomedical areas. Furthermore, in order to attract interest and support from a broad range of funding agencies, it will be necessary to have clear and specific plans.

A closer communication between marine biologists with their wide range of knowledge of the sea biota and the biomedical researchers, knowledgeable of the problems of human disease, is important for the full realization of the use of marine organisms for biomedical research.

After consultation with a few leaders in marine biology and biomedicine on how best to increase this communication, it was decided that the next step would be to meet with a larger group of scientists with these same interests to explore further the status of the art and the health of the marine biological laboratories, and the scientific and organizational problems involved.

The National Institute of Environmental Health Sciences has found that one of the most successful ways to gather information on the current state-of-the-art is to convene conferences of this kind. Over the last three years, NIEHS has sponsored conferences in a wide range of topical areas such as PCBs, PAEs, vinyl chloride, heavy metals, asbestos, and mutagenesis. A second, but equally important aspect of these conferences, is that they provide a neutral forum for the researchers, the applied and the regulatory scientists from government, universities, and industry to come together frequently to discuss sensitive regulatory issues. Also, because of the conviction that scientific issues frequently require extensive public debate, and because of the keenly felt obligation to inform the public of NIEHS's activities and their meaning, representatives are invited from the press to join as participants in these conferences.

In summary, NIEHS serves two major functions: to support and conduct fundamental research in important and relevant areas, and to serve as a hinge pin, linking the diverse, and yet compatible interests of the scientist and the public.

Also, NIEHS communicates with the American citizen through his elected representative. The importance of the Congress to stimulate, support and criticize Federally supported biomedical research programs cannot be overstated. It seems clear that the National Institutes of Health, as it is today, is the result of 30 years of nonpartisan support of the Congress.

Congressional Liason

Harley M. Dirks (Labor and Health, Education and Welfare of the Senate Appropropriations Subcommittee): The interest of Senator Magnuson and his colleagues in marine biology and the environment is indicated in recent hearings of the appropriations and commerce committees. There is a need for well thought-out program plans presented in language understandable to the layman, keeping in mind national priorities and the strong competition for the Federal dollars for such programs, if additional support is sought.

Marine Species as Models for Human Disease

Marine Species as Models

Stewart G. Wolf (Marine Biochemical Institute, University of Texas, Galveston, Texas): Marine organisms offer a potentially rich source for models of human functions and diseases for which there are several important examples (e.g., Homer Smith's work on kidney function and the use of the squid axone in neurophysiology) but about which there is really only fragmentary knowledge at present of the possible useful systems. The unused advantages in the phylogenetic approach to the study of functions and disease as a supplement to the study of function by interruption of processes in common laboratory animals by surgery or inhibition by toxic chemicals was cited. For example, there is recently derived, strong evidence that the fundamental lesion in diabetes mellitus involves a disorder of cell to cell communication between alpha and beta cells of the islets of Langerhans. Hence it would be important to establish as a baseline the preglucagon insulin regulatory mechanisms. Such fundamental information on diabetes may be available from the study of primitive fishes before and after the evolutionary appearance of glucagon. The cyclostomes, in which endocrine and exocrine pancreas are conveniently and completely separated, appear to possess insulin secreting beta cells but no alpha cells and no glucagon. Alpha cells and glucagon make their appearance among teleosts.

Over the more recent eras of biological evolution a few new molecular structures, like glucagon and its sister secretin, have appeared, but for the most part Nature has used, with minor variations, the same substances and the same strategies of molecular interaction. Thus it is often feasible, through the study of relatively simple organisms, to elucidate regulatory mechanisms that operate in the complex systems of man. Few would doubt that the understanding of regulatory processes is the key to understanding the fundamental mechanisms of disease.

Until recently the question asked with respect to pathophysiology was, "What happens?" Now the question is, "How does it work?" There is a wide discrepancy in our understanding of "How it works" in the various systems of the body. Little is known of the metabolic regulatory processes of the liver, for example, and much is known in the case of the kidney. Because of the intelligent exploitation of marine organisms by Homer Smith and his colleagues at Mount Desert, much of the complex behavior of the human kidney has been elucidated. Although scientists are still largely in the dark in the search for therapeutic measures to reverse the processes of kidney disease, it is understood pretty well how they come about.

Marine organisms are beginning to yield comparable dividends for students of the nervous system. Thus some of the complex interactions of neurons, glia and neurotransmitter systems that spell psychiatric and neurologic disease in man are beginning to be unravelled through systematic study of the simpler circuitry of marine invertebrates and fishes.

The prediction was made that the next system that will begin to yield secrets will be the endocrine system. Already several published reports suggest a profitable switch to a phylogenetic approach to the study of endocrine regulation.

Additional examples cited included sekoke, a syndrome virtually identical to diabetes mellitus, which occurs among carp in Japanese fish farms. It is due to the fact that the carp are fed silk worm pupae rich in unsaturated fatty acids. The disease has been produced experimentally by simply feeding fatty acids and can be prevented by pretreatment with the antioxidant vitamin E (α-tocopherol). This model provides an extraordinary opportunity to manipulate metabolic regulators by dietary changes.

The relationship of thyroid to other glandular functions, especially in relation to sexual maturation has been studied in several teleosts including the Indian catfish, *Heteropneustes fossilis*, and during seasonal and temperature changes in other teleosts.

Calcitonin production has been studied in lung fishes. Lung fishes have also provided an insight into the very exciting area of neurohormonal interaction and neural regulation of endrocrine activity in the activation of these hibernating fish.

Further evidence on endocrine regulation by neurosensory cues has been adduced in certain gastropods in whom gonadal development is triggered via stimulation of external chemoreceptors.

Spectacular neurohormonal relationships have been described in the migrating Pacific Salmon by O. H. Robertson, Wexler, and their collaborators. During migration from the ocean to fresh water upriver for spawning, the fish developed a rapidly progressive adrenal hypercorticism with many features of Cushing's Disease hyperlipidemia and extensive arteriosclerosis. After spawning, the fish all died. The arterial lesions contained very little lipid but resembled closely the fibrous plaques of human arteriosclerosis. Interestingly, the males were as much affected as the females. Castration appeared to protect both males and females against the fulminating arteriosclerosis. In 1968, Van Citters and Watson described the development of similar arterial lesions in steelhead trout (*Salmo gairdnerii*) as they swam from the sea to fresh water to spawn. In contrast to the salmon, however, not all of them died. Some of the trout were able to swim back to the sea. In them the arterial lesions regressed and disappeared. It should be possible by maintaining this fish in a controlled environment to manipulate the process of arteriosclerosis development and its reversal.

While a good deal is known of what goes on in man in the complex metabolic factory called the liver, little is known of the responsible regulatory mechanisms. One organism with a simpler, but essentially similar, metabolic factory to man is the shark. The liver of the shark, architecturally similar to that of man, appears to perform more of a storage than a metabolic processing function. It is capable of excreting unconjugated bilirubin in the bile, however. It stores large amounts of fat, some (containing squalene) apparently used to control buoyancy and some (triacyl glycerols and wax esters) to support energy requirements. An understanding of the regulatory processes involved in these functions, will have important relevance for human pathophysiology. The shark liver is also the site of extra medullary hematopoesis. Some of the biosynthetic activities carred out in the enormously complex human liver are undertaken by the stomach and intestine in the shark. Thus the shark liver offers a somewhat simpler chemical laboratory for study. Nevertheless, what biochemical transformations take place in the organ seem to be similar to those that occur in the human liver. Among the biosynthetic functions of the shark liver is one, the synthesis of trimethylamine oxide, a substance with an apparently osmoregulatory function, via TMA oxidase, a system closely akin to the detoxifying mechanisms of human liver for foreign nitrogenous compounds. The liver of the shark in his normal sea water environment synthesizes urea but not albumin in more than trace amounts. A high concentration of urea is retained in the blood to effect osmotic balance. The shark can be acclimatized to a fresh water environment however, and when he is, the concentration of urea in the blood falls because of increased urea clearance, not a decrease in urea synthesis, and amazingly the liver begins to manufacture a significant amount of albumin. The study of this capability through experimental manipulation would certainly have great relevance to human hepatic disease.

The deep sea anglers live in depths from one thousand to several thousand feet, where very reduced numbers make finding a mate difficult. When males do encounter a female they bite into her flesh and attach themselves permanently. Ultimately a sort of placenta-like cross-circulation develops and, as the male gets his nourishment from the connection with the female, his body and organs, with the exception of the testes begin to atrophy, so that ultimately the male becomes nothing but a sperm producing appendage to the female. Angler fishes have been caught with as many as three or four males attached. The important question for medicine is why the foreign tissue—the male is essentially a graft—is not rejected. Does the angler fish offer an important model for the study of tissue transplantation and rejection?

It was concluded that the marine environment constitutes for the biomedical researcher a veritable gold-mine of useful models that have only just begun to be exploited.

Brain Cells from Marine Animals as Models for Studying Epilepsy

A. O. D. Willows, (Friday Harbor Laboratories, University of Washington): A model system was described in which the excitation effects of drugs and other experimental factors can be studied on a single neuron of a sea slug under controlled conditions. This model makes possible studies at the cellular level that are not possible in mammals and therefore opens the way for resumed progress in solving problems of these kinds that are of direct importance to man.

It is a well known and an extremely useful fact that the fundamental characteristics of normal healthy nerve cells from creatures as diverse as man, mollusks and medusae, are virtually identical. Indeed, an understanding of most basic nerve cell electrical phenomena has been gained almost exclusively from bizarre creatures such as squid. The fact that certain disease conditions of the brain cells of man are recognizable in the neurons of very simple organisms is nowhere near so widely recognized nor utilized. For example, the convulsive bursts of electrical impulses that recur in primates suffering from various forms of epilepsy, can be elicited from the neurons of sea slugs (nudibranch mollusks). Furthermore, some of the drugs that produce (and, in other cases, relieve) the disease condition in these creatures have similar effects in primates, encouraging increased confidence that the underlying causes of the disorder are the same in both cases. What is most significant, however, is the fact that certain sea slugs offer some extraordinary opportunities for research into the basis for, and by extension, the cure of these disorders.

The unique advantages from the point of view of researchers are that the neurons in sea slugs are relatively large, and even recognizable and reidentifiable as individuals under experimental conditions. Investigators are able to impose precisely controlled drug exposure conditions on particular neurons while monitoring and analyzing the resulting electrical activity with microelectrodes that penetrate the cells. This permits determining whether epileptic, convulsive bursts originate from regenerative excitatory interactions between neurons, or from electrical instability caused by sudden brief opening of specific ion channels, for instance.

Investigations are under way to determine why such neurons are hyperexcitable, why they produce impulses synchronously with others and why waves of electrical excitation with brief high frequency burst of impulses occur. Preliminary results indicate that unusual instabilities occur in the gating mechanisms of channels that regulate ion movements through nerve membranes; there may be significant increases in the effective electrical coupling between neurons that are treated with epileptogenic drugs; and the electrical resistance of the membranes of such neurons is substantially increased. There phenomena, either individually or in combination, are possible contributing factors in the convulsive activity of neurons. It is likely that model systems involving marine animals for the study of epileptic or convulsive disorders will play an important, if not crucial role in the near future in determining the physiological mechanisms that underlie these diseases.

Environmental Carcinogenesis and Mutagenesis

Environmental Pollution and Fish Papillomas

H. F. Stich (Cancer Research Centre, University of British Columbia): A chemical hazard to the genome of man and animals may manifest itself in the development of mutations, congenital anomalies, and cancers which appear only after long latency periods. Without obvious clusterings of diseases in space and time, an increase in their frequency can be readily missed. Thus preventive measures can only be introduced at times when large population segments are irreversibly affected. Recent observations indicate that marine organisms can provide sensitive and useful models for studies of this important problem area. Furthermore, it appears that the marine and river environment is becoming widely contaminated by carcinogens, mutagens and teratogens and merits more attention in this regard also. The reported high frequencies of skin papillomas in several flatfish species (up to 58%, Stich and Acton), European eels (up to 28%, Peters), gobies (up to 14%), melanomas of *Argyosomus argentatus* (up to 55%, Kimura), tumors of the parabranchial gland of cod (up to 44%, Forrester), gonadal tumors of carps (up to 60% of particular age groups), and lymphosarcomas of muskellunge (up to 20% , Sonstegard), exemplify the seriousness of this problem.

The use of easily detectable skin tumors among bottom-feeding fish as an early and economical warning device is being considered and its feasibility in a large-scale monitoring program is being explored. The epizootiological studies must be supported by laboratory experiments to separate the action of chemical compounds from that of oncogenic viruses and cancer-predisposing genes. Furthermore, the biological indicator system must be complemented by a chemical analysis of key carcinogens and mutagens in sedentary accumulator organisms in order to trace the source of contamination.

The extent of contamination of marine organisms and sediments by carcinogenic and mutagenic polycyclic aromatic hydrocarbons (PAH) has been examined by isotope dilution and gas chromatographic techniques. The degree of contamination of mussels (*M. edulis* and *M. californianus*) by benzo[a]pyrene (BaP) is closely correlated with the degree of human activity in the vicinity of the sampling site. Mussels from uninhabited areas show contamination ranging from 0.0 to 0.2 μg/kg (wet weight), from the outer Vancouver harbor: 2–4 μg/kg, from a poorly flushed inlet with light industry 30–60 μg/kg, and from marinas and wharf areas up to 60 μg/kg. Comparable levels were found in other organisms. Elevated levels of BaP were present in sediments near a sewage outfall. Motorboat marinas and creosoted wharf structures appear to represent major sources of PAH in the marine environment. Edible mussels growing on creosoted pilings show BaP levels as high as 214 μg/kg, far in excess of the standard of 1 μg/kg recently adopted by the Federal Republic of Germany for smoked foods. The measurement of benzo[a]pyrene in mussels, which are ubiquitous and easy to sample, may be very useful in a large-scale screening program for carcinogens in the marine environment.

Histopathological Effects of Oil Pollutants on Marine Life

Paul P. Yevich (National Marine Water Quality Laboratory, Narragansett, R. I.): The effects of various kinds of fuel oil on shell fish (mussels, clams) were reviewed. Random specimens were collected from the vicinity of several oil spills over a 4-yr period along the East Coast and from similar laboratory exposures of scallops, oysters and lobsters. The fact that knowledge in the area of histopathology of marine organisms is very sparse and poorly developed—there is little baseline information to guide such studies—was emphasized. However, most specimens studied showed extensive amebocyte infiltration and/or possible tumor development, especially in the gonadal and connective tissues both from field and laboratory exposures. It seems clear that fuel oil is deleterious to shellfish; that they might be used for pollution monitoring purposes and perhaps for the study of the development of tumors of environmental origin. It seems evident that there is great need for systematic and extensive studies in this area.

Discussion, C. J. Dame (Laboratory of Pa—thology, National Cancer Institute, NIH): Some reservations were expressed as to whether these lesions were really tumors; however, there was no question that they should be further studied. The lack of knowledge in the area of histopathology in lower animals was also emphasized. NCI has no water laboratories for experimental animals. There should be a collection point and collaboration in the evaluation of such slide materials.

Registry of Tumors in Lower Animals

John C. Harshbarger (Smithsonian Institution, Washington, D.C.): The needs for more attention to this area was again emphasized. Some benefits which could be expected to accrue from studying neoplasms in invertebrates and cold-blooded vertebrate animals were enumerated.

Neoplastic diseases reduce the value of commercial species, increase the costs of harvesting healthy survivors, and at their worst could directly and indirectly weaken a population to the point of extinction. It is not known, if neoplasia has been a significant factor in any animal becoming extinct, but at least one endangered species, the green sea turtle, (*Chelonia mydas*) frequently is found with dermal fibromas that can exceed 14 cm in diameter.

New carcinogens may be revealed. The carcinogenicity of the aflatoxins was discovered as a result of an investigation on a hepatoma epidemic in hatchery rainbow trout (*Salmo gairdneri*) in the early 1960's. Aflatoxins are produced by *Aspergillus flavus*, a mold that rapidly grows on warm, damp cereal products. Moldy soybean and peanut products were the sources of the aflatoxins in the fish food. Aflatoxin is a potent carcinogen for rodents and has been linked epidemiologically to human cancer. This has resulted in Food and Drug Administration regulations which protect American consumers.

Such studies may indicate carcinogens in the environment. In the freshwater environment, a population of tiger salamanders (*Ambystoma tigrinum*) living in a sewage settling pond becomes neotenic and has a 50% incidence of neoplasms of the skin. Most of the neoplasms are either epidermal papillomas, intradermal fibromas, or intradermal melanophoromas, but dermal fibrosarcomas and invasive dermal melanophoromas also occur. In the marine environment, white croakers (*Genyonemus lineatus*) feeding near sewage outfalls along the Southern California coast are subject to oral epidermal papillomas, while croakers collected away from the sewage discharge areas do not have tumors. While both of these examples suggest that there is a carcinogen in the sewage, no such agent has been identified in either case.

Animals uniquely suited to the study of various mechanisms of carcinogenesis may be discovered. Herpes viruses cause or have been linked to Marek's lymphoma in chickens and cold sores, mononucleosis and Burkitt's lymphoma in people. The leopard frog renal adenocarcinoma should be an excellent model for the study of how herpes viruses cause cancer. Leopard frogs (*Rana pipens*) are easy to maintain, have external fertilization, and the ova and embryos are amenable to microsurgery. The tumor occurs in very high incidence, is transplantable, and the virus is easily harvested.

Two lower animal cancers are caused by allelic genes at one locus, both of which are especially suitable to genetic study: an invasive, transplantable, neuroblastoma in the insect, *Drosophila melanogaster* and a malignant melanoma in the platyfish–swordtail hybrid. The intensity of the effect of the melanoma gene is influenced by modifying genes at five different loci.

In studying the influence of immunity, it has been shown that "b" lymphocytes produce less immunoglobulins as the phylogenetic scale is descended from mammals through amphibians, bony fish, cartilaginous fish, and jawless fish. In invertebrates, there are no b lymphocytes. This suggests interesting possibilities for studying the influence of selected immune factors on tumorigenesis.

Lower animals may be used to develop superior methods to screen new chemicals for carcinogenicity. Less than half of the new chemicals that go into major production are screened for carcinogenicity due to the excessive cost and other requirements of rodent and primate test systems. Various lower animals offer many possible advantages of sensitive and clear cut responses to carcinogens and/or mutagens, high fecundity, natural cloning, simple genetics due to a relatively small genome, easy low cost maintenance, etc. Such studies could also identify possible vectors of neoplastic viruses. Under experimental conditions, mosquitoes have been shown capable of transmitting several tumor viruses. Obviously, more studies should be done, especially with blood sucking ectoparasitic arthropods from pets, farm animals, and birds.

Some carcinogenic compounds are concentrated in invertebrates and lower vertebrates, suggesting the possibility that these compounds could be passed up the food chain to humans. A good example of biological magnification occurred when Japanese fishermen developed mercury poisoning from consuming fish from Minamata Bay.

Many of the chemotherapeutic agents already in use were derived from natural products. Based on the almost limitless diversity of plant and animal life, we have barely scratched the surface in testing natural products for antitumor activity. In conclusion, lower animals offer many excellent opportunities for significant contributions to the understanding, treatment, and prevention of cancer. Some assistance in such studies could be provided by the Registry of Tumors in Lower Animals (RTLA) which he directs at the Smithsonian Institution with support from the National Cancer Institute. The Registry was established in 1965 for the purpose of studying neoplasms and related diseases in invertebrate and poikilothermic vertebrate animals. Specimens with cryptogenic and induced lesions are collected from natural habitats, zoological parks, aquaria and laboratory experiments. Specimens are logged in, photographed, processed as required, studied grossly and microscopically, and the findings are communicated to the contributors. If the Registry prepares the material histologically, a set of slides is sent to the contributor along with the diagnosis.

Currently several thousand specimens are listed among the 1100 accessions in the Registry's collection, 50% of which have neoplasms. Two-thirds of the neoplasms occur in bony fish and the remainder are divided (in descending numbers), among the mollusks, amphibians, reptiles, arthropods, cartilaginous fish and jawless fish. The preponderance of aquatic animals having neoplasms are bottom-feeders and bottom-dwellers, the so-called rough fish and the bivalve mollusks. Presumably these scavengers, grazers, and filter-feeders receive more exposure to environmental carcinogens than carnivores and surface feeders. While unconfirmable reports of neoplasms in other invertebrate phyla occur in the literature, no good examples have been received by the Registry.

Pertinent information from the specimen reports and from 2800 papers in a comprehensive library on tumors in lower animals is being abstracted and computerized. This information includes the author; collector and/or contributor; reference; taxonomy; habitat; general type of disease; system, organ and cell of origin; diagnosis; transmissibility; inducibility; physiologic parameters; and etiology.

When specimens are received that appear to be good research models for furthering the understanding of the neoplastic process, research projects may be initiated with the consent of the contributor. Currently the Registry is participating in studies of papillomas in fish and salamanders and in nonneoplastic disease in clams.

Investigators are invited to contribute to the Registry's collection by submitting examples of induced or cryptogenic neoplasms, preneoplastic conditions or lesions of a presumptive neoplastic nature that need confirmation. As there is an indistinct boundary between neoplastic disease and the process of inflammation, repair and regeneration, examples of these processes are also useful in establishing points of reference. Specimens are accepted alive, fixed, in tissue blocks, and on slides. Frozen material is usally unsatisfactory for the preparation of good histologic material.

An indexed, cummulative catalog of the Registry's holdings through 1973 has been prepared and is maintained current through annual supplements. The catalog and supplements, which also contain general information on the activities of the Registry, methods for fixing and shipping specimens, tables showing distribution of neoplasms among various animal groups and examples of noteworthy accessions, are available on request.

Human Health and the Marine Environment

The DDT Problem as Prototype

G. M. Woodwell, (The Ecosystem Center, Marine Biological Laboratory, Woods Hole, Mass.): The use of DDT in the U.S. was virtually abandoned after a series of exhaustive reviews in the courts of New York and Michigan, and before hearing examiners in Wisconsin and Washington. The basis for restriction was that DDT is broadly toxic and virtually uncontrollable once released into the environment. It is vaporized, can be transported by air, and deposited in the oceans; its fat-solubility guarantees that it will be accumulated in living systems, including man.

World-wide use of DDT is probably now as high or higher than during the early 1960's when U.S. production was at a peak. However, the bulk of use has shifted from the temperature zone to the tropics. DDT concentrations in the temperate zone oceans appear to be declining; concentrations in the biota of the temperate zone are declining as well. Certain bird populations drastically reduced by DDT accumulations appear to be recovering, confirming the wisdom of the restriction of use.

Recent studies suggest that the residence time of DDT residues in the atmosphere is much shorter than thought previously. Appreciable photochemical decay must occur and may be an important mechansim for removing DDT from circulation. The heavy use of DDT in the tropics where air movement is upward and poleward exposes airborne residues to intense solar radiation for a longer period than airborne residues in the temperate zone and may reduce the world-wide hazards.

However the DDT problem appears to be far from resolved; there is likely to be a similar problem with other chemicals. Such problems require a world-wide type of study, and, present methods and procedures are inadequate for the job. The needs are for a sound appraisal of total use, a comprehensive estimate of biospheric burdens, and further detailed data on biotic effects (if only to test the arguments of DDT's promoters). DDT remains a challenge to our toxicological approach to environmental questions, to the assumption of thresholds, to our systems for appraising biotic effects, and to the political systems that must regulate such toxins.

It is disturbing that there are powerful efforts to resume the use of DDT in the U.S. before our information base is adequate.

Biomedical Aspects of Red Tide Blooms

E. J. Schantz, (Food Research Institute, Uni—versity of Wisconsin): One class of marine organism (the dinoflagellates) which produce a variety of toxins that may get into the food supply of man through shellfish was discussed. These algae under certain conditions not well understood can bloom out to Red Tide proportions along coastal areas.

Gonyaulax catenella is the predominate poisonous dinoflagellate along the Pacific coasts of the United States and Canada and *Gonyaulax tamarensis* is the predominate poisonous one along the northeast Atlantic coast of the United States and the coasts of Canada and the countries along the North Sea. Shellfish such as clams, mussels, oysters and scallops that feed on these organisms become very poisonous and when these shellfish are consumed by people a paralytic disesase results that is severe and may cause death within a few hours. The paralytic poison produced by *G. cantenella*, called saxitoxin, has been purified and its chemical structures established. It is a substituted tetrahydropurine with a molecular weight of 372 and paralyzes by inhibiting the passage of sodium ions through nerve and muscle cell membranes, a process necessary for the propagation of an impulse. The poison produced by *G. tamarensis* acts similarly, but its chemical structures appears different than that of saxitoxin and so far has not been established. There is no known antidote for these poisons.

There are other poisonous dinoflagellates that produce poisons of a different nature. One of these is *Gymnodinium breve*, that causes such destructive Red Tide along the Florida coasts. Blooms of this organism causes massive fish kills. Something produced by these organisms is aerosolized by the ocean spray and causes respiratory disturbances in people along the coast. The chemical nature of these poisons is not well established.

Red Tide is unpredictable, creates a sanitary nuisance (fish kills); leads to great economic loss in use of beaches and shellfish (no process has been found to free shellfish from these toxins, e.g., clams) and is a threat to human health. There is need for more research on how to predict and prevent these episodes and to better understand the health effects.

Filter-Feeding Shellfish as Disease Vectors

R. Di Girolamo (Department of Biology, College of Notre Dame, Belmont, Calif.): The problems arising from the fact that filter-feeding shellfish take up and retain bacteria and viruses and therefore become disease vectors for man were discussed. Filter-feeding shellfish—primarily to oysters, mussels, and clams—feed by selectively filtering and concentrating small particles of matter from large volumes of water. Among the particles concentrated, and subsequently ingested, are bacteria and viruses capable of producing disease in humans.

Microbes known to be concentrated by shellfish include the agents responsible for bacterial dysentery and typhoid fever as well as those responsible for producing gastroenteric disturbances. Shellfish have also been implicated in transmitting one virus disease, infectious hepatitis.

The problem presented by polluted shellfish serving as vectors of disease is not a new one. Early research proved that shellfish which had been residing in sewage polluted waters could serve as vectors in the transmission of bacterial dysentery and typhoid fever. Shellfish involved in outbreaks included commercially grown as well as privately collected animals.

There is now an effective shellfish control program which monitors shellfish growing areas and licenses growers and shippers. Due to control programs, recent bacteriological outbreaks have been relegated largely to handling of shellfish by asymptomatic disease carriers or the illegal harvesting and sale of oysters and clams collected from polluted water. In addition to monitoring, modern research programs have been concerned with determining effect of temperature on bacterial survival in shellfish, development of more efficient methods for evaluating bacterial pollution of shellfish, and developing methods for eliminating bacteria on a commercially feasible scale. Results obtained have shown that bacteria can survive in shellfish at storage temperatures (10°C) and may reproduce at higher temperatures. Use of the fecal coliform group of bacteria as indicators of fecal pollution by man and animals appears sounder under most circumstances. How valid these organisms are as indicators in shellfish that have been frozen may be questionable. Use of ionizing radiation and depuration seem promising as means of removing bacteria from oysters and clams.

The first outbreaks of shellfish borne viral infectious hepatitis were reported from Sweden between 1955 and 1956. Since this time a number of other outbreaks have occurred in Europe and America. Research has shown shellfish capable of accumulating a number of viruses. Under experimental conditions maximum contamination of shellfish occurs within the first 24 hr of exposure. The digestive tract seems to be the major site of viral accumulation, but apparently there is no replication.

Uptake of viruses by shellfish may be ionic in nature involving attachment to a specific variety of shellfish mucus.

Studies have shown poliovirus to survive for 30 days in oysters held at refrigerated temperatures (5°C) and for up to 12 weeks in frozen samples. Viruses are also capable of surviving processing of shellfish, the rate of survival depending upon processing method and temperature. They are also resistant to the inactivating effects of gamma radiation. Doses of radiation sufficient to produce reduction in titer (400 Krad) produce changes in the shellfish rendering them unpalatable.

Depuration of shellfish in free-flowing, sterile seawater appears to be a valid means of eliminating bacteria. Experimental data also indicates this process effective in removing viruses; however, more research is needed.

Filter-feeding shellfish may not be the only ones capable of accumulating and retaining bacteria and viruses. Recent investigations have shown West Coast crabs also capable of accumulating viruses either directly from polluted water or from feeding on contaminated shellfish. Viruses can survive in crabs processed by simple boiling. Accumulated viruses will survive in contaminated chilled or frozen samples of edible crabs for periods of 5 days to one month, depending upon storage temperature. To date there have been no confirmed reports linking crabs to viral diseases, however, crabs and shrimp have been implicated as vectors in outbreaks of gastroenteritis caused by *Vibrio parahaemolyticus*.

Present shellfish monitoring programs should be continued and expanded to include surveillance of other types (i.e., crab and shrimp). Depuration studies should be encouraged and supported on a larger scale. More financial and technical assistance is needed.

Metabolic Cycles for Toxic Elements in the Aqueous Environment

J. M. Wood, (Freshwater Biological Institute, University of Minnesota): How toxic metals get into and move through the environment to, in some cases, serve an essential biological function but in others deleterious function, was discussed in detail. Movement of metals and their relocation in advanced industrial societies, represents a major environmental problem today. The movement of mercury alone has caused major disasters in Japan, Pakistan, Iraq, Sweden, Canada, and the U.S.A. The incidents in Japan and Iraq have resulted in the death or irreversible mental illness in over 4000 people. In order to fully understand the movement of toxic metals through geochemical cycles into biological cycles, followed by bioaccumulation and toxicity in the central nervous systems of higher organisms, it is important to understand the general principles of how metals are moved.

Before the evolution of organic matter, in the form of primitive life on this plant, a number of geochemical cycles existed for inorganic salts and metals. These geochemical cycles were perturbed by biological activity. Some time later, biochemical cyclyes evolved for the elements. Bacteria developed the capability to move metals out of geochemical cycles into biological cycles; so that certain important minerals were made available to higher organisms including man. The movement of cobalt in Vitamin B_{12} represents an excellent example of this process. Microorganisms hold the most important position in the movement of toxic elements.

Bacteria have the ability to adapt to environmental stress. For examples, if bacteria is exposed to toxic elements, they develop mechanisms to resist toxicity either by the selection of mutants or by excluding toxic elements from the cell. In addition to moving essential elements from the geocylces, bacteria have the ability to move toxic elements into biological cycles. For example, the movement of mercury salts by their bacterial conversion to methylmercury, followed by the bioaccumulation of methylmercury in the central nervous system of humans, provides a frightening examples of this process. Methylmercury is deadly poisonous to the central nervous systems of higher organisms.

As with other natural processes the concentrations of methylmercury available for bioaccumulation will depend on the rate of synthesis of methylmercury versus its rate of degradation. Vitamin B_{12} and cytochromes appear to play important roles in alkylation and reductive dealkylation respectively. Furthermore, cytochromes appear to be important in the reduction of metal ions of higher oxidation states to the elemental form, e.g.,

$$H^+ + NADPH + M^{++} \rightarrow NADP^+ + M^\circ + 2H^+$$

where NADPH is the reduced pyridine nucleotide and M^{++} denotes metal ion. Based on this research, metabolic cycles can be demonstrated for a number of toxic metals and metalloids in biological systems. These cycles depend to a large extent on the B_{12} dependent conversions of inorganic species to organometallic species which are capable of bioaccumulation.

Thus B_{12} holds a unique position in terms of alkyl-transfer reactions in aqueous systems. This reaction goes extremely rapidly with several metal ions, and also with molecular iodine to give methyl iodide and $Co^{(III)}$ I as products. This reaction with iodine probably explains why methyl iodide is found in significant concentrations at the surface of our oceans.

Drugs From the Sea

Marine Biomedical Research Today

Ara Der Marderosian, (Philadelphia College of Pharmacy and Science, Philadelphia, Pa.): Marine sources of useful or potentially useful drugs and what is known of their chemistry and biological action was reviewed. While our present knowledge is substantial, it is only a beginning of what the marine environment holds for development in this area.

In reviewing the attractiveness of the marine environment as a storehouse of biologically active substances, it was cited that some 71% of the earth's surface is covered with water and that the oceans teem with animal life of great diversity, with well over 500,000 species in 30 phyla. Yet when we examine the studies on these organisms, we find that only a few percent have been closely examined for biologically active compounds out of thousands reported to be toxic. Even less have been evaluated to the point of determining their chemical and pharmacological characteristics.

Notwithstanding, there is already a significant number of long used "classic" pharmaceuticals from the sea currently in use. These include agar from algal species in the genera, *Gelidium, Gracilaria* and *Hypnea*; the alginates from species of *Fucus* and *Macrocystis*; carrageenan from *Chondrus*; cod liver oil and sodium morrhuate from the codfish, *Gadus morrhua*; protamine sulfate from the sperm and mature testes of salmon, *Oncorhynchus* species; spermaceti from the sperm whale; ichthammol from bituminous schists containing fossil fish; and numerous others.

However, it was pointed out that while these are important, they do not represent the newer and more significant agents which are currently being developed or which lie just over the horizon. These newer agents portend great new discoveries and a more intimate understanding of the workings of nature. The more recently discovered molecules are in many cases "exotic" or unique biodynamic models on which the synthesis of whole new classes of drugs may ultimately be based. They represent leads for improving our current medical armamentarium in all the traditional pharmacological classes of drug action, and, in fact, hint at newer activities heretofore unknown. The scientific literature abounds with examples of antibiotic, antifungal, and antiyeast properties possessed by the marine bacteria; anthelmintic, antiviral, anticoagulant, antispasmodic, and ichthyotoxic substances from the marine algae; antibiotic, aggregation factors and growth regulators from spones; neurohumoral and anticoagulant agents from jellyfish; sperm immobilizing, neuromuscular blocking and neuroactive substances from echinoderms (starfish, sea urchins, and sea cucumbers); antiviral, neuromuscular active, growth inhibiting and hemolytic agents from mollusks; insecticides from marine annelids; cardioactive agents from arthropods; and numerous neuroactive compounds in the various classes of fish, amphibians and reptiles.

As examples of some of the newer drugs which are currently marketed or are close to market, one may cite the cephalosporium family of antibiotics originally discovered in the marine fungus, *Cephalosporium acremonium*; the anthelmintic, kainic acid from *Digenea simplex*; the antipeptic and antiulcer agent carrageenan from *Chondrus* species; the anticoagulant, hemostatic, radioprotectant and pharmaceutical adjuvant, alginic acid from *Fucus* and *Macrocystis* species; the antiviral and antitumor nucleic acid derivatives from the marine sponge *Cryptotethya crypta*, which served as models and led to the ultimate synthesis of *D*-arabinosylcytosine now marketed as cytarabine and used in the treatment of leukemia; the powerful insecticide nereistoxin from the marine annelid, *Lumbriconereis heteropoda* which served as a prototype for the synthesis of 1,3-bis-(carbomoylthia)-2-*N,N*-(dimethylamino) propane, now marketed as Padan in Japan; the powerful neuroactive drug, tetrodotoxin from the puffer fish which has been used clinically to relax muscular spasms and as a palliative in terminal cancer; and the prostaglandin derivative, 15-epi-PGA_2 which has been isolated from the gorgonian *Plexaura homomalla* and converted to active isomers (PGE_2 and PGF_2-alpha) which have great potential as agents useful for birth control, prevention of peptic ulcers, treatment of asthmatics, etc. These are but a few of the exciting leads which are in various stages of development.

Another parameter of assessing the state-of-the-art in a field is the number and kind of research publications which appear in the scientific literature. There is little doubt that in the past decade that the number of these articles as well as texts and related compendia have increased significantly. In addition, several symposia proceedings have been published, including a recent position paper on marine biomedical research.

In concluding, it was noted that there will never be an end for the need for developing new drugs. The marine environment offers one of the best promises for finding new and different biodynamic agents in addition to leading to an understanding of cell processes in greater diversity and detail than now possible. We should not forget that close to 50% of our prescription drugs on the market in the U.S. today still owe their origin to drugs from natural sources (e.g., antibiotics, reserpine, digitalis, steroids, etc.) of terrestrial origin. Continued studies in the marine environment certainly will augment this further.

Marine Biological Laboratories

Organization, facilities, staff, research, and educational programs, and means of support of twelve marine biology laboratories were described by their directors.

The Scripps Institution of Oceanography has been a unit of the University of California since the 1920's; it offers the Ph.D. degree in Oceanography, Marine Biology and Earth Sciences and has excellent laboratories and facilities for marine biological research including the ship Alpha Helix which is considered a national resource. Scripps has a research staff of 66 and academic faculty of 60, 18 of whom work in biomedical areas in close cooperation with the medical school; an annual budget of 31 million dollars, of which 10% is for biology. Support is received from the University of California and grants from the National Science Foundation, the National Institutes of Health and Energy Research and Development Administration. There are ongoing research programs in neurophysiology, thermoregulation, nutrition, development, metabolic regulation, barobiology, and behavior. These include digestion and metabolism in the food chain of marine organisms, metabolism of halogenated hydrocarbons, cholesterol synthesis and metabolism in the swim bladder, metabolism of wax in marine organisms, serum enzymes and lipoproteins in fish, antifreeze glycoproteins in Antarctic fish, metabolism of natural and pollutant hydrocarbons, and bioelectric studies of phenomena in fishes. All of these areas have a direct bearing on understanding human health and disease.

The Duke University Marine Laboratories (DUML) is an interdepartmental and interuniversity facility covering 15 acres. It has 19 buildings, a research ship and facilities for marine sciences (oceanography and biology). It is located at Beaufort, North Carolina; has a full-time staff of 11, 20 graduate students and 60–80 undergraduates; is supported by Duke University and about $0.5 million dollars in grants from NSF and NIH. There are research programs in molecular biology and basic marine levels, examples: adaptation of marine protein molecules to urea; amino acid sequences in fish muscle; and allergy and fish proteins.

Dauphine Island Sea Laboratory, Dauphine Island, Alabama was established in 1971 and is operated by a consortium of 18 schools in Alabama and provides facilities for under graduate and graduate education and research in oceanography and marine biology. It has a fulltime staff of four, 25 graduate students and 120 students during summer sessions. Facilities include 35 acres, a ship, a new biology laboratory and dormitories—all new developments. The laboratory is supported by the State of Alabama and by grants from NSF and NASA. There are research programs under way in biochemistry and physiology; transport of metals in ecosystem; effects of pesticides and metals on marine organisms; pathological organisms in oysters; stress and cardiovascular effect in fish; lipid transport in the marine catfish as a model for lipid transport in salmon.

The Marine Biological Laboratory, Woods Hole, Massachusetts, was founded in 1888. It is a self-governing corporation of 500 biologists who elect a Board of Trustees whose Executive Committee and a part-time Director operate the laboratories and living facilities. The primary function of the organization is to make available to professional biologists and students, from all over the world, marine animals and other special research facilities needed for studies in the area of marine biology. Until recent years, the laboratory has operated primarily as a summer research and educational institution, providing a rich intellectual environment through the many research programs and the lectures, seminars and brief courses by the many senior scientists in residence. The laboratories are not an official part of any academic institution and grants no degrees; however, many universities give graduate credit for research and short-course work done here. While the laboratories are still mostly a place where the investigator rents space to do "his own thing" in the summer (500 investigators and students), there are now considerable year-around activities (approximately 15%) and there are plans to further develop this aspect of the program. The original research emphasis at Woods Hole was on developmental biology but now there is much research in the area of sensory physiology, ecosystems and genetics, all with a heavy component of molecular biology. However, because of the broad research interests of the many visiting scientists, there are programs in many areas of marine biology.

Progress in all aspects of marine biology would be greatly accelerated if it were possible to rear and maintain a greater variety of marine organisms under laboratory conditions and not be dependent upon sea harvest methods for supplies. The Woods Hole laboratories hope to increase their activities in this area. The nearby facilities of the Woods Hole Oceanographic Institution, also self-governing and also a unit of the National Marine Laboratories (fisheries), adds to the total of marine facilities in the area. Support for the Marine Biological Laboratory (approximately $2 million a year) comes mainly from grants and contracts, either direct or through rental paid by individual investigators. There is a small endowment from private sources.

Mount Desert Island Biological Laboratory, a smaller, self-governing laboratory (one-tenth the size of Woods Hole) located at Salisbury Cove, Maine (near Bar Harbor), was founded in 1898. Its organization, staff, functions and support are much like the Marine Laboratory at Woods Hole. It is located where there are up to 13-ft tides (average 10.5 ft) and has available both Gulf Stream and Artic specimens. This laboratory has a distinguished history in marine biomedicine in which prominent names such as Marshal, Homer Smith, Shannon, and others are associated. Renal physiology and membrane transport have been prominent research areas for years, however, work also goes on in enzymology, cancer chemotherapy, and spinal fluid formation and effects of pollutants. Studies are basic research oriented, there is no ecology program. The summer population of students and senior investigators may number near 100 and have for years included a goodly portion of M.D.-biologists. There is a year-around total staff of 15–20. There is no formal teaching program; however, there are seminars and preceptor teaching. There is a small endowment for fellowships; otherwise support is obtained by individual investigators through the grant mechanism, (NIH, NSF).

Mote Marine Laboratory, Sarasota, Florida, is an independent, nonprofit, twenty-year–old research institution dedicated to basic research in marine biology; located 45 miles south of Sarasota, Florida. There is a resident staff of about 40 (10 of whom are Ph.D.'s) with excellent facilities and space for visiting scientists and students who wish to work under the direction of a staff scientist. The research program is divided into five areas: microbiology, neurobiology and behavior; estaurine ecology and environmental health; biology of sharks; and biomedical studies. However, space is available for senior scientists and their assistants to work on any problem appropriate to the environment. Sea and estuarial species appropriate to the area are available. There are ongoing projects on Red Tide, effects of DDT on fish and birds, meaning of catfish sounds, blood brain barrier, sodium pump on shark glands, neurotransmitter and receptor substances, shark deterrents, polyamine synthesis in sea urchins, chemotherapy, tumors in fish and invertebrates, and several areas in ecology. Operational costs come from private contributions, membership dues, and modest charges to visiting investigators for laboratory space. Specific research programs are funded by grants from individuals, foundations and government agencies.

C. V. Whitney Laboratory, The University of Florida, St. Augustine, Florida is a new, one-year-old marine biology laboratory located on a 7-acre tract between the coast and intercoastal waterway about 1.5 hr from the University in Gainesville. It provides 10,000 square feet of well-equipped biological laboratory space, faculty quarters, dormatories and conference rooms. Dr. Gurin plans a senior resident staff of 8–10 with space for visiting scientists, assistants and graduate students. The Director reports to the Vice President for Academic Affairs. They offer degrees through departments of the University in Gainesville. Programs are planned or underway in chemoreception (e.g., chemical structure and transfer of information); reproductive physiology of fish and fish culture and genetics. Dr. Richard Smith, Professor of Pathology, is developing a program on the phylogenetic development of immumoglobulins, lymphocytes, virus receptors (e.g., herpes virus in mollusks) and bacterial endotoxins.

The program has a molecular biology and biomedical emphasis. About 60% of support comes from the State budget and 40% from grants.

Virginia Institute of Marine Science, Gloucester Point, Virginia, is located near the York River and shore area. It has a staff of 400 (90 scientists), provides research facilities and graduate education through the University of Virginia and William and Mary College, and has dominant commercial interests and functions. The interests are in five general areas: changes in shore areas; biological research; wetlands; geology; and marine resources. Some of the programs are: clam and lobster management; migration patterns; new species of oysters, clams and crabs; aqua culture; diseases of clams and oysters; herring and shad problems; decay of wetlands; pesticide and metal survey of bay area; biological effects of oil spills; mineral resources of shelf; water circulation patterns; water quality; and effects of sewage on marine life. There is a small amount of biomedical research in the areas of coli, virus, salmonella in oysters, mechanism of filtration and cleansing in oysters and clams, herpes virus and protozoan host and toxins of the jelly fish. The Institute is supported by State and by grants and contracts.

Skidway Institute of Oceanography, Savannah, Georgia is a part of the University system of the State of Georgia, and is about five years old. It has a staff of 100 (12 faculty) and a research program orientation which emphasizes environmental quality of the shore and the Savannah River and its effect on the biota. Two projects of special interest are the effects of pollution and recovery of the biota trapped in a 70,000 liter porous bag suspended in the ocean or river; and the metabolic pathway of hydrocarbons (oil) through the food chain. It has been found that crustacea metabolize hydrocarbons, while mollusks do not. There are also programs in aquaculture (shrimp and catfish farms) and lipoprotein systems relative to phyla.

Friday Harbor Laboratories, University of Washington, Friday Harbor, Washington is about 70 years old and serves the faculty and visiting scientists of the University of Washington. It is located about 80 miles north of Seattle, on 500 acres of land or more and provides year-around facilities including a rich source of species, from oceanic as well as shore waters. Operational philosophy is much like that at Woods Hole: it is staffed by independent investigators with no local guidance. It is 80% state-supported and receives 20% support through grants. The character of the programs depend upon the investigator. There are ongoing projects on neurophysiology and pharmacology, nonmuscle protein contraction, and jelly fish protein as a calcium indicator.

The School of Marine and Atmospheric Sciences, University of Miami, Miami, Florida is organized and operates as a graduate school of the University, providing degree opportunities in a broad research and teaching program in marine science including biology, geology and geophysics and chemical and physical oceanography and atmospheric sciences. There is a faculty of approximately 50, with approximately 20 in the biological area. Fully developed laboratories and research vessels are located within ready reach of the Gulf and West Indian Ocean; habitats and fauna are of a wide variety including sand beaches, mud and turtle grass flats, mangroves, coral rock shores and living reefs. While there is no special biomedical program there are many research programs that are relevant to this area and there is potential for expansion in, toxins of man of war; nutrition, growth and toxins of Red Tide; physiology of sharks; respiratory system of turtles; phylogeny of immunity; virology (e.g., herpes in turtles); effects of environmental pollutants; and mari cultures. Support comes from University and private sources, research contracts, and grants. The recent decrease in Federal source of support is causing great difficulties as it is with other marine laboratories.

The Marine Biomedical Institute, University of Texas Medical Branch, Galveston, Texas came into being in 1970 with Dr. Stewart P. Wolf as Director. There is a staff of 17, which is closely coordinated with eight departments of the medical school as well as with other campuses of the University of Texas, Rice and the University of Houston. It operates with the help of a National Advisory Council and is developing a program directly concerned with biomedical problems. In addition to their own facilities, which includes vessels and hyperbaric chambers, the facilities of the medical school are being used. An aqua medic group for response to undersea accidents is operational. Programs in diver physiology, neurobiology, cardio-vascular and neurophysiology, renal function and monitoring of pollutants from sewage and other sources are underway. They expect to work closely with health departments and with the "Texas Tower" groups. There will be emphasis placed on man in the sea. Support is about 40%

from the State, 20% private, and 40% from grants from NIH, NSF, and Office of Naval Research (ONR).

National Marine Fisheries Service (N.M.S.), U.S. Department of Commerce while not directly biomedical, these programs are nevertheless relevant. N.M.S. (formerly Bureau of Commercial Fisheries) operates seven research centers and 27 laboratories (1,000 people) which conduct a comprehensive program of research, development and services for the commercial fishing industry of the United States. The purpose of these activities—many of which are carried out cooperatively with industry and the states—is to strengthen the industry and to conserve resources. Many of the facilities are located near and cooperate with some of the marine biology programs previously described, e.g., Woods Hole, Galveston, Seattle, Duke, LaJolla, etc. Research programs are conducted on diseases of marine organisms (shellfish and salmon) and the effects of pollutants (oil, metals, pesticides), shrimp and mollusk culture and gas bubble disease.

Summary and Discussion of Common Problems

In addition to the information and comments during the formal presentations and discussions on present activities and resources, research and training, potential problems and needs in marine biology/biomedicine area, further discussions took place on these subjects as a final agenda item. In addition, several participants sent letters containing additional comments, the consensus of which is also included in this summary. No formal conclusions were reached or attempted in this first meeting, but material was provided that will be useful for the development of a more complete and logical treatment of the subject. However, certain points needing further attention did emerge.

Marine biology and the great diversity of marine organisms represent a large unused potential for the provision of models that would be helpful in the study of human disease, as indicated by many examples presented at this conference. Marine organisms possess a vast repertoire of adaptations valuable as models for study of human metabolism and its disorders. Models are important because the simplicity of their structural or metabolic specialization permits study of a single problem at a time. In contrast, the human or laboratory animal often conceals its functions by the complexity of their interrelationships.

Other areas in which marine biology contributes to the health sciences include atherosclerosis regulation; nutrition and its metabolic disorders; calcium regulation and osteoporosis; toxicology and drug detoxication processes; milk metabolism and sensitivities; thermoregulation and adaptations to environmental stress; anoxia and protective processes during birth, diving, and circulatory impairment; metabolic adaptations to natural toxic and difficultly processed substances; dental development and adhesion; fat digestion, storage and mobilization; hepatitis and its marine carriers; mucus production and regulation, vitamin A production and function in intestinal function, pulmonary function and disorders (hyaline membrane disease); endocrine regulation (salmon calcitonin in human therapy); prostaglandin therapy for abortion in obstetrics, etc., derived from marine gorgonians and cytosine araboside (therapy for leukemia) from marine sponges.

The development of marine biomedicine will not be realized unless biomedical scientists, knowledgeable about human health problems, learn more about marine biology, and marine biologists, knowledgeable about the great variety of creatures of the sea, learn more about biomedical problems and needs.

The number of scientists knowledgeable in both areas is small and has developed in the past mainly by a few biomedical scientists incidently becoming interested in marine biology. A more organized and effective means needs to be found to foster such developments.

Marine biomedical research and training will have to be done where a large variety of marine creatures are available—this means in marine biology laboratories strategically located throughout the country to provide organisms from diverse environments (oceanic, shore, cold and warm temperatures, estuarial, etc.).

There are among the existing laboratories those that could provide this research and training environment, however, they will need some further development of general marine biology facilities and marine biomedical programs. This development would require funds and program plans that are not now available.

Marine laboratories serve many functions, e.g., research and training in general biology; research and training in physical oceanography; research and services for developing and conserving sea resources; research relative to monitoring of pollution; and marine biomedicine. It seems logical that support for marine sciences, as a whole, will necessarily have to have a broad funding base which could come from many sources.

Present marine laboratories are supported from a variety of sources, e.g., private grants or endowments, educational institutions (state and private universities) and grants and contracts on a project-by-project basis from Federal and state agencies (e.g., National Institutes of Health, National Science Foundation, National Oceanic and Atmospheric Administration, etc.). In many cases, staff find their own support for summer work usually by one or more of the above means. In most cases there is a lack of long-term, stable sources of income. Plans have to be made on a year-to-year basis and even then success depends critically on the personal interests and dedication of the staff and visiting scientists.

While present sources provide project-type funds on an intermittent basis—and, hopefully, should continue to do so—there are many costs in operating a marine laboratory that cannot practicably be funded with intermittent project funds; to do so means inefffficient, inadequate facilities and uncertain services, and a lack of development of long-term plans. Project funds do not support the development of the common use of new facilities nor the maintenance of old laboratories, libraries, vessels, power plants, aquaculture facilities, etc., nor the key year-around staff necessary to keep the plant going; nor the exploratory research that is necessary to open new areas. Furthermore, the recent constriction of Federal project grant funds tends to decrease support for long-term projects that may be critical to the solution of difficult biomedical problems in favor of projects of lesser importance but of immediate "pay off". This is causing increased problems for marine biology laboratories. It seems clear that some type of core-support for marine biological laboratories is necessary if marine biomedicine is to develop. The criteria and source for such support is not clear and needs to be developed.

Project-type support for marine biology/marine biomedicine would probably increase and be made more objective if funds were made available under that program title and a review process developed involving both knowledgeable and interested health scientists and marine biologists.

At the present time, marine laboratories have no regular means of communication with each other about mutual program interests, opportunities, or problems. Furthermore, there is even a lesser means of developing public understanding including legislative, executive and government agencies, about the importance of such programs to the future of health research and protection. A number of suggestions were made to improve communications, e.g., a series of seminars or workshops on selected problems of mutual scientific or administrative interest, (e.g., aquaculture, models, model systems, etc.); formation of an association of marine laboratories; development of an up-to-date list of marine laboratories including a brief description of their organization, scientific programs, etc.

There is a clear need to better define the scope and goals of the area called "marine biomedicine" and its relationship to other aspects of marine sciences. Some participants commented that the subject areas represented in the agenda of this meeting were a good start. It was suggested that an additional area might be diving physiology, particularly as related to offshore oil drilling activities.

The need and importance for a program plan for marine biomedical research and training, expressed in terms understandable to the layman, would seem necessary as a basis for requests for program support irrespective of the sources. Dr. David P. Rall, Director, National Institute of Environmental Health Sciences, and the conferees agreed that an informal group be formed of Drs. Cyrus Levinthal, Columbia University, New York, Roy P. Forster, Dartmouth College, A. O. Willows, Friday Harbor Laboratories, University of Washington, and A. A. Benson, Scripps Institution of Oceanography, to further pursue this idea.

It was suggested that, since Federal support for various aspects of marine sciences will come from interested agencies, it might be well to have a future conference at which each agency would discuss the type of program it might support.

Since the development and welfare of marine biomedicine is so closely linked with other activities in which marine laboratories are involved, (e.g., oceanography, ecology, fisheries, etc.) it was suggested that a conference similar to this one should be held to develop a broader information base and a common approach to program needs and problems.

It seems unlikely that the number of students, choosing careers in marine biomedicine or related marine biology areas, will increase over the recent past unless funds for the support of such training is forthcoming. Assuming availability of training funds—although the present situation does not seem encouraging—there still remains the problem of how to attract more biomedical scientists in developing an interest and knowledge in marine biology. Further questions arise as to career opportunities. The need for expert manpower seems clear due to the increased emphasis on: pollution and its effects on man and the ecosystems; preparation and evaluation of impact statements; and the increased use of marine organisms as models in biomedicine, for monitoring the environment and for the development of environmental health criteria standards. It is not yet clear how these demands will relate to career opportunities, however, a postdoctoral training program in this area seems essential if these needs are to be met even at a token level.

Several participants emphasized that one of the most important needs in promoting the greater use of marine organisms in health research is the development and maintenance of aquaculture techniques and facilities. It is technically possible to culture more and more marine organisms for a full-life cycle and therefore to open up studies on "biochemogenesis" and organogenesis. This is important for basic science as well as for applied research on such problems as teratogenesis, mutagenesis, and carcinogenesis. The possibility of large broods of sea creatures available at all stages of development, from fertilization to adults and in a variety of phylogenetic states, opens up experimental opportunities not available in usual laboratory animals. Such techniques and material are certain to make basic contributions to the above critical areas of human concern. Such marine facilities need long-term funding to produce the required research and development.